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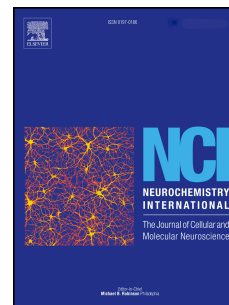
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**“NEURO-NUTRACEUTICALS: THE PATH TO BRAIN HEALTH
VIA NOURISHMENT IS NOT SO DISTANT”**

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Abstract

In this Special Issue on “Nutraceuticals: Molecular and Functional Insights into how Natural Products Nourish the Brain”, the editors bring together contributions from experts in nutraceutical research to provide a contemporary overview of how select chemically identified molecules can beneficially affect brain function at the molecular level. Other contributions address key emergent issues such as bioavailability, formulation, blood brain permeability, neuronal health and inflammation that impact upon how nutraceuticals ultimately leverage the brain to function better. Whilst nutraceutical is used as marketing term, it has no regulatory definition, and there is a continuing need for licensing authorities to ensure that adequate guidelines exist pertinent to the safety to guide consumers internationally. In terms of the benefit of nutraceuticals is it clear that some naturally occurring molecules can be advantageous to both the young and aged brain, and that they have actions that ultimately can be directed to aid either in the improvement of cognition or in the management of debilitating neurodegenerative and neuropsychiatric conditions.

Key words

Nutraceutical, traditional medicine, neurodegeneration, inflammation, development, ageing

This Special Issue grew out of the awareness of the Editors that the basic and clinical research underpinning how nutraceuticals improved brain function during development, ageing and disease was growing in quality such that the focus was increasingly on cellular and molecular targets that ultimately leveraged improved brain function. What is truly amazing is the spectacular recent growth of interest in this topic from a neuro-perspective given the overall surprising lack of endeavour targeting the brain relative to the nutraceutical field in general. A PubMed search for nutraceuticals turns up more than 50,000 articles, but less than 2,000 of these are linked to the brain. However, encouragingly some 50% of these latter publications addressing brain function have appeared in the last five years. Everyone is living longer, dementia and Alzheimer's disease threaten, and people the world over want to enjoy life in their latter years. Keeping the brain healthy by use of natural products, increasingly advocated by nutritionists, proponents of alternative medicine, the popular press and social media, thus emerges as a goal the populace at large wants to achieve.

Nutraceutical is a term coined in 1989 by Dr. Stephen L. De Felice (Founder and Chairman of the Foundation for Innovation in Medicine, New Jersey, USA) from nutrition and pharmaceutical. The Nutraceutical Research and Education Act (1999) of USA seeks to 'promote research into the health benefits of dietary supplements, medical foods, and other foods. It demands sound scientific evidence of safety and effectiveness in order to fulfil its statutory mandate to protect and promote the public health'. Nutraceuticals represent vitamins, amino acids, minerals, trace elements, etc. which consists of about 60 groups of compounds identified so far. Within the nutraceutical category there are more than 1000 compounds, and typical examples include resveratrol from grapes, genistein from soy proteins, lutein from kiwi fruit and broccoli, lycopene from tomatoes, bromelain from pineapple, and organosulphur compounds from Allium vegetables (e.g. garlic, onion, leeks; Powolny & Singh, 2008).

Whilst a key aim herein was to focus on investigations of chemically identified molecules isolated from traditional medicines, a further aim was to overview the background and modern horizons of how nutraceuticals might be used to sustain brain health in daily life and during debilitating pathologies. We also sought to provide an overview of the limitations to the exploitation of nutraceuticals and to give some proper consideration to the metabolism, bioavailability and blood brain permeability of molecules that might exert beneficial actions on brain. The editors in assembling this Special Issue, "Nutraceuticals: Molecular and

Functional Insights into how Natural Products Nourish the Brain”, recognized that the time was right for an overview of this expanding field. However, the project has grown so rapidly, with incredible enthusiasm from authors internationally, that the issue will now be published as two parts with the second volume appearing in early 2016. Overall, we hoped this Special Issue would provide a timely overview of this emerging field and map key future directions for neuro-nutraceutical research.

Nutraceuticals - some historical perspective

In hindsight, the in vogue acceptance and pre-eminence of nutraceutical related research is not surprising. As suggested above, we all want or seek to improve brain health be it in aging or disease. The Oxford Dictionary defines “nutraceutical”, a term derived from both nutrition and pharmaceutical, as “another term for functional food” with functional food being “a food containing health-giving additives”. Basically, any part of a food providing health benefits, including the prevention and/or treatment of disease. From the perspective of prehistoric medicine in the ancient world on all continents, plants have been used in the treatment of medical conditions through human history. Historically, one can trace a path linking apothecary, herbalism, ethnopharmacology, phytotherapy, and alternative medicine to nutraceuticals. In some cultures the primitive concept of prevailing illness was seen as a punishment of the gods and the evolution of therapy often had both “magical” and “instinctive” components involving both vegetables and medicinal plants, and remedies of animal and mineral origins (Albarracin, 1985). Of course, European herbal medicine and therapeutic methods benefited greatly from the transfer of traditional knowledge from Asia, the Middle East and the Americas. With the rational use of medicines the apothecarist became a pharmacist and eventually the principles of drug action, therapeutics and modern drug development with clinical trials ensued. In hindsight it is interesting to recall that drug is from the French “drogue” meaning dried herb. Nevertheless, such “traditional medicine” continues today.

The history of the Indian tradition on healing art is rich in varied traditional healing procedures; roughly *Ayurveda*, *Unani*, *Siddha* and *Ashtavaidya* systems of medicine merging into the major ones. Ancient texts of classical Ayurveda are *Charaka Samhita*, *Susrutha Samhita* and *Ashtangahrdayam*, which date back to 371 – 287 BC (Menon and Spudich, 2010). A Traditional Knowledge Digital Library (TKDL) was created by the Council of

Scientific and Industrial Research, Government of India, to provide information on traditional knowledge existing in the country, in languages and format understandable widely (Chaudhry and Singh, 2012; Kidd, 2012). Not surprisingly, there was a similar tradition in China and the Compendium of Materia Medica, also known as *Bencao Gangmu* or *Pen-tsao Kang-mu*, is a Chinese materia medica work written by Li Shizhen during the Ming Dynasty. The Compendium of Materia Medica is regarded as the most complete and comprehensive medical book ever written in the history of traditional Chinese medicine, consisting of 1,892 entries. It lists all the plants, animals, minerals, and other items that were believed to have medicinal properties. Li Shizhen completed the first draft of the text in 1578, after conducting readings of 800 other medical reference books and carrying out 30 years of field study (Yaniv and Bachrach, 2005). Chinese herbal medicine was transferred to and further developed in Japan becoming *Kampō* medicine, which has aspects relevant to the management of nervous system conditions. Interestingly, some herbal medicines in Japan are regulated as pharmaceutical preparations and integrated into the Japanese national health care system (Sugaya et al., 1997).

So where did neuro-nutraceutical research begin in modern neuroscience? Indeed here, it is hard to go past the almost legendary publications by Jim Joseph and colleagues (Joseph et al., 1998, 1999) describing behavioural and cognitive improvements after blueberry, spinach, or strawberry dietary supplementation. Having heard the late Jim Joseph speak, his charismatic style of presentation engendered great enthusiasm in the audience such that one would want to add neuro-nutraceuticals to your diet. Joseph's background in neurochemical pharmacology represented a solid launching pad for his work and made him very conscious of the role of oxidative stress in brain injury and neurodegenerative conditions. His work mentions the earlier success of increased dietary vegetables and fruit rich in antioxidant activity in reducing the incidences of ischemic heart disease and cancer. Additionally, there is also reference to the diversity of potentially bioactive molecules contained in vegetables and fruit, noting the presence of various phytonutrient antioxidants, including flavonoids. In hindsight, the initial focus upon antioxidant activity is hardly surprising as at this time oxidative stress was receiving massive attention as a causative mechanism in brain pathologies (Simonian and Coyle, 1996; Higgins et al., 2010). Indeed flavonoids have long attracted much attention in human nutrition and Kuhnau (1976) in his classical review noted their mention relevant to vitamin research by Nobel Prize winner Szent-Gyorgi and colleagues (Bentsath et al., 1936). Interestingly, at the time of publication of Joseph's work,

Catherine Rice-Evans across the Atlantic in London was attacking flavonoid biology after many years of experience in probing their chemistry and subsequently published notable accounts with neurochemical colleagues of their neuroprotective ability versus injury in cultured neurons (Schroeter et al., 2000 & 2001).

Diverse actions of nutraceuticals

Nutraceutical related research of molecular actions follows from the concept that traditional medicines or tribal practices offer nutritious agents that cure diseases. The goal then is to elucidate how bioactive molecules from these sources might make the brain healthier and in this volume we have a number of exciting basic studies that represent the prototype of how this field needs to evolve. For example, **geniposide** (contained in *Gardenia* fruit; Chinese medicine) attenuates insulin-deficiency-induced acceleration of β -amyloidosis in an APP/PS1 transgenic model of Alzheimer's disease (Zhang et al.). Neuroinflammation plays a prominent role in the pathophysiology of many neurological conditions and is considered a genuine therapeutic target by the pharmaceutical industry, so it is hardly surprising that the search for novel anti-inflammatory agents continues apace amongst nutraceuticals. **Oxymatrine** (derived from root of *Sophora*; Chinese herb), reported to have anti-inflammatory actions, elevates anti-oxidant mechanisms with consequent decreases in the extent of damage observed after hypoxic-ischaemic brain injury (Zhao et al.). **Apocynin** (root of *Picrorhiza kurroa* (*Scrophulariaceae*); traditional Indian medicine (Ayurveda)), also believed to have anti-inflammatory actions, was found to attenuate the cholesterol oxidation product-induced programmed cell death in neuronal cells by preventing production of reactive oxygen species and depletion of glutathione (Lee et al.). **Curcumin** (*Curcuma longa*; traditional Indian & Chinese medicine) produced beneficial effects in chronic epilepsy by attenuating glial activation and suppression of the activation of cytokines and chemokines (Kaur et al.). Flavonoids and polyunsaturated fatty acids (**eicosapentaenoic and docosahexaenoic acids**) alleviate the inflammatory response of activated microglial cells and these anti-inflammatory actions appear to be beneficial in modulating age-related memory decline (Vauzour et al.). **Resveratrol** has a similar action against microglial activation, although multiple actions on silent information regulator 1 (SIRT1), AMP-activated kinase (AMPK) and nuclear factor (erythroid derived 2)-like 2 (Nrf2) may contribute to its beneficial effects in models of ischemic stroke and traumatic brain injury (Lopez et al.). Garlic (*Allium sativum*) has long been considered a remedy for human diseases and **S-allyl cysteine**, the most abundant

compound in aged garlic extracts, has various neuroprotective actions likely mediated by anti-oxidant actions perhaps via Nrf2, but more recent observations suggest additionally a panoply of anti-inflammatory effects (Colin-Gonzalez et al.). **Allicin**, another component of garlic, effectively blocked neuronal injury via an action on sphingosine kinase 2 and demonstrated protective effects in a rat model of middle cerebral artery occlusion even after delayed administration (Lin et al.). **Crocin**, a plant colouring pigment (*Crocus sativus*) previously shown to possess anti-inflammatory actions, was found to attenuate endoplasmic reticulum stress in a cellular model of Parkinson's disease (Zhang et al.). Finally, Ashwagandha (*Withania somnifera*) has been extensively employed in traditional medicines as an aphrodisiac and it led to the upregulation of release and expression of gonadotrophin-releasing hormone supporting its use as a preparation for improvement of sexual performance and fertility (Kataria et al.).

Flavonoids – old nutraceuticals but much interest in new actions

In reality, it was no surprise that the actions of flavonoid-like molecules attracted much attention since these are well documented to have neuroprotective actions be it through their diverse actions, including those as free radical scavengers and/or activators of key signalling cascades (Mercer et al., 2005; Williams et al., 2004). Despite significant advances in our understanding of the biology of flavonoids over the past 15 years they are still mistakenly regarded by many as acting simply as antioxidants yet flavonoids exert modulatory effects in cells independent of classical antioxidant capacity through selective actions at different components of a number of protein kinase and lipid kinase signalling cascades. Furthermore, flavonoids exert actions on mitochondria, interfere with pathways of intermediary metabolism and there is good evidence for specific flavonoid interactions with GABA_A receptors (Johnston). Indeed work during the 1990s drew attention to flavonoids as 'a new family of benzodiazepine receptor ligands', but flavonoids possess at least two distinct mechanisms via a variety of sites in the GABA_A receptor (Johnston). With respect to potentially protective actions in dementia, flavonoids are likely to combat neuronal dysfunction and toxicity by recruiting anti-apoptotic pro-survival signalling pathways, increasing antioxidant gene expression, and reducing amyloid β (A β) pathology (Williams et al., 2004; Williams and Spencer, 2012; Cox et al., 2015). There is however, a lack of consensus as to the precise identities of the flavonoids capable of exerting these effects, partly because flavonoids have poor bioavailability and are extensively metabolised *in vivo*,

but also because most *in vitro* studies use concentrations that are at least 100 times higher than those found following dietary administration. Alternatively or concurrently, there is emerging and compelling evidence derived in part from human studies suggesting that flavonoids can positively affect peripheral and cerebrovascular blood flow (Rendeiro et al.) and this indirect mechanism influencing neurovascular coupling may explain some of the observed effects of flavonoids on plasticity and cognition, even in the absence of good brain bioavailability.

Quercetin, found in vegetables and fruit, potentially has both pro- and anti-oxidant actions, with the latter effects eliciting redox regulation of proteins, transcription factors and a broad range of kinase-dependent signalling cascades, some of which are linked to cellular survival mechanisms (Dajas et al.). Complex absorption and metabolic steps after oral intake make it likely that nutraceutical additive actions of quercetin will be best served by its pharmaceutical formulation to expedite optimal delivery and such a preparation effectively produced recovery of brain activity with improved breathing, motor and feeding behaviour in perinatal hypoxia (Blasina et al.). In a landmark study (Janssen et al.), undertook the first detailed examination of perinatally supplemented dietary flavonoids during the gestational and postnatal period on brain structure, cerebral blood flow, cognition, and brain metabolism in mice. There were subtle alterations in brain structure, locomotor activity and spatial learning, suggesting that the benefits of dietary flavanols may increase with advancing age. The naturally occurring BDNF-mimetic, flavonoid **7,8-dihydroxyflavone** (*Godmania aesculifolia*, *Tridax procumbens*, primula leaves), rescues cognitive deficits and may represent a novel treatment for schizophrenia, autism, Rett syndrome and foetal alcohol disorder (Du and Hill). Over the years many studies have examined the potential benefits of the consumption of tea, which contains various flavonoids, and the major green tea component (-)epigallo-catechin 3-gallate (EGCG) efficiently crosses the blood brain barrier - these polyphenols are active in cellular and animal models of Parkinsonism suggesting green tea may be considered as an anti-Parkinsonian, natural-origin beverage (Dutta and Mohanakumar).

Emergent issues: bioavailability and the concept of one molecule with multiple Nutraceutical actions

Indeed for polyphenols in general, including quercetin, improving bioavailability entails efficient *in vivo* transport across the blood-brain-barrier and biochemical stability with improved half-life via modern drug delivery approaches considered essential for optimal efficacy in brain (Pandareesh et al.). The application of nanotechnologies to clinical neuroscience is in its infancy, but nano-enabled drug delivery systems pass through the blood brain barrier and improve delivery of drugs such as natural antioxidants to the central nervous system to allow therapeutic management of neurodegenerative conditions (Sandhir et al.).

Trans-resveratrol and **pterostilbene** are two nutraceuticals where improved bioavailability would also be beneficial as these promising bioactive agents improve brain health, having diverse actions against oxidative stress and inflammation, and appear from clinical trials to be relatively well tolerated (Poulose et al.). In this volume we feature two articles where the investigators have succeeded in using contemporary drug delivery methods to deliver nutraceuticals - drug delivery via nanoparticles and related technologies is certainly a way forward to achieve adequate brain concentrations of potentially advantageous nutraceuticals. Thus Blasina et al. achieved an impressive beneficial outcome in perinatal hypoxia with a nanosomal delivery of **quercetin**. **Curcumin** micelles prevented mitochondrial dysfunction and improved its bioavailability some 10-40 fold in murine plasma and brain relative to native curcumin (Hagl et al.).

Modern drug development is strongly focused on the guiding principle that a drug should possess just one site of action, with little or no additional effects that might compromise its selectivity. However, the literature is full of examples where clinical approved drugs act upon multiple targets and many attempts have been made to develop pharmaceuticals that are bi-functional in their actions. Here it may be worth re-interpreting the view of Joseph et al. (1998) that “the whole is more than the sum of its parts” i.e. maybe it is not the overall actions of multiple nutraceuticals in a functional food that provide health benefits and treat a disease condition, but the multiple beneficial actions of a single “effective” nutraceutical? In the modern context of the molecular and cellular neuroscience of neurodegenerative conditions and brain injury, not only are multiple mechanisms involved (e.g. oxidative stress, excitotoxicity, protein aggregation, disturbed proteostasis, etc and their downstream effects), but neuronal injury is accompanied by inflammation (recruitment of micro-/macrogial signalling), and altered cerebral blood flow in concert with changes in the blood-brain-barrier (see Fig. 1). So it would not seem heretical to propose that one naturally occurring and

bioavailable substance in a mix of potentially bioactive molecules might have multiple ameliorative actions on brain function and/or pathology by interacting with multiple targets.

Thus in this context, flavonoids can positively affect peripheral and cerebrovascular blood flow, which may represent an indirect mechanism by which dietary flavonoids could impact upon brain function. Here improved efficacy of cerebrovascular coupling could potentially increase neuronal activation and synaptic plasticity leading to improvements in cognitive ability – indeed cerebral blood perfusion declines in aging and other neurological disorders (Rendeiro et al.). In related, novel work **fisetin**, known to have many central actions (direct anti-inflammatory & antioxidant activities, increases glutathione, activates neurotrophic signalling), was shown by fluorescence imaging in living mice after peripheral administration to be rapidly distributed to blood vessels of the brain followed by a slower dispersion into the brain parenchyma (Krasieva et al.). Some phytochemicals activate adaptive stress response pathways, which are also recruited by exercise and energy restriction, implying these molecules may improve brain health and reduce the risk of neurodegenerative disorders. Emerging evidence suggest that neurohormetic phytochemicals can enhance removal of proteopathic proteins by activation of pathways that minimize oxidative damage and bolster bioenergetics (Murugaiyah and Mattson). The interface of nutraceuticals with brain bioenergetics is an emerging issue worthy of attention. Boosting energetics may improve cognitive function and **creatine**, long known to have nutraceutical-related actions (Wallimann, 2007), appears to have the potential for cognitive enhancement, particularly in conditions where baseline bioenergetics are compromised (Rae and Broer). Relevant to the issues introduced above, Ng et al. also make the point that some naturally occurring alkaloids (and nutraceuticals) may be beneficial since the sum of their actions may arise from multiple targets. Indeed, in this context promising clinical results of galantamine and memantine combination therapy support multi-target-directed ligands as a new treatment strategy for etiologically complex diseases such a neurodegenerative conditions. These authors found that although **rhynchophylline** had multiple pharmacological actions, its potency as an inhibitor of the receptor tyrosine kinase EphA4 translated to rescue of hippocampal synaptic dysfunction in a mouse model of Alzheimer's disease AD (Fu et al., 2014). So seemingly the multiple beneficial actions of a single nutraceutical can improve brain health, but the important corollary is that there should be scientific evidence of safety.

Nutraceuticals, their promise and regulatory issues

The National Center for Complementary and Integrative Health of the National Institutes of Health (USA) conducted a nationwide survey on American children's use of natural products such as melatonin, Echinacea, probiotics, as well as on the use of mind and body approaches of yoga, chiropractic, massage, and complementary health approaches between 2007 and 2012. The survey revealed natural product use in the United States has shifted since 2007, with certain products such as fish oil and melatonin more popular, and some such as glucosamine/chondroitin, echinacea, and garlic, being dropped. Fish oil use was the top natural product among adults, and children, followed by melatonin, the use of which increased substantially from 2007 to 2012 (<http://nccih.nih.gov/NHIS2012>).

There are limitations and worries about the use of nutraceuticals, which are widely available, but loosely regulated. They are not strictly under any regulations unlike pharmaceuticals, and therefore business houses may create undesirable products for consumption for selfish gains. Low bioavailability is another worry (*vide supra*), which is heightened when low doses are recommended for nutraceuticals which are noxious chemicals termed as “neurohormetic phytochemicals” (Murugaiyah and Mattson). Lack of scientific validation, overzealous marketing gimmicks, wide media support, etc are other public concerns. Animal studies and clinical reports are available for adverse reactions, and reactions following multidrug interactions. Typical cases are allylisothiocyanate, a nutraceutical acting as a carcinogen in higher doses (National Toxicology Program, 1982; Waddell, 2003), and an unusual adverse effect of a nutraceutical containing tiratricol causing paralysis (Cohen-Lehman et al., 2011).

One issue for regulatory authorities is that commercially available products claimed as possessing “nutraceutical activity” do not generally undergo traditional randomized, placebo controlled, blinded clinical trials and thus proper consideration has not been given either to toxicology or to the pharmacokinetics including metabolism and bioavailability. Moreover, many nutraceuticals could be considered as undefined extracts wherein the molecular actions and targets, and their “drug interactions” are undefined. This creates a significant problem as in some cases it is resulting in the indiscriminate marketing of food supplements and nutraceuticals on the basis of unproven neuroprotective effects, and positive health claims have been made about nutraceuticals and supplement that have extremely poor brain bioavailability. Indeed, it is notable that there are no preventative nutraceutical recommendations for preserving brain health by any major health organization and regulatory

agencies have not given any positive opinions for nutraceuticals or supplements to improve brain function during aging or neurodegeneration. Thus, hardly surprisingly nutraceutical as a commonly used in marketing term has no regulatory definition. There is little financial incentive for the pharmaceutical industry to progress this area, so a logical course of action would seem to be the participation of companies (loosely grouped under the industrial banner of natural health and wellbeing) involved in the provision of complementary medicines. The challenge for the community must be to work towards randomized placebo-controlled trials that will be the gold standard to confirm the effect of nutraceuticals on brain function. However, such trials may be impossible to conduct for nutraceuticals targeted to alleviate brain aging and cognitive decline, where subtle effects might add up over decades and be strongly influenced by individual differences in diet and nutrition. One finds in many published articles the concept that the interactions among various classes of chemicals present in foods may contribute to their potent “nutraceutical actions”. In fact Joseph et al. (1998) used the expression “the whole is more than the sum of its parts”.

Despite the forgoing sentiments about the need for properly conducted clinical trials and regulation the story is not all doom and gloom. The prospect of future success in the field of neuro-nutraceuticals continues to capture the imagination of many neuroscientists. With stunning advances in neuroscience in the 21st century, there has been a remarkable growth in the identification of targets that provide therapeutic benefit in degenerative conditions, and neurodevelopmental, psychological and psychiatric disorders. Since many natural products used in traditional medicine have long been known to exert beneficial actions on diverse brain functions and often the active principles have been identified, nutraceuticals are potentially ripe for the plucking in terms of entering the developmental drug pipeline. Certainly there is also case for high throughput screening at identified targets using modern technologies. The work reported here with quercetin, curcumin, fisetin, allicin and oxymatrine represents important advances and indicates that naturally occurring molecules can be beneficial to both the young and aged brain, and that they have actions that ultimately can be directed to aid in the improvement of cognition and in the management of debilitating brain pathologies.

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Figure legend

Fig. 1. Potential benefit of nutraceuticals on brain dysfunction. Nutraceuticals are food, or part of a food, and will give health benefits in addition to nutrition to provide better health and/or minimize pathological effects. Molecules contained therein provide medicinal value, and bridge the gap between food and prescribed medicine. Nutraceuticals provide more than nutritional value, and the synergistic actions of certain ingredients subtly influence key cellular signalling that favours improved neuronal function. Medicine is an independent molecule designed to have specific action at one target, but at higher doses and over long-term use these molecules could adversely affect normal cellular functions, possibly leading to cellular toxicity. Such events may exacerbate mechanisms (dysfunctional bioenergetics, oxidative stress, DNA damage, inflammation, neuronal injury) that contribute to normal ageing and cellular crises, and ultimately brain damage. Nutritious food containing molecules with medicinal value can alleviate these disruptive mechanisms by correcting deranged cellular signalling, and thus nutraceuticals provide the added value of helping to repair cellular damage, thereby improving brain health.

